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GEMCITABINE, FLUDARABINE AND MELPHALAN AS A NOVEL REDUCED-INTENSITY CONDITIONING REGIMEN FOR ALLOGENEIC STEM CELL TRANSPLANTATION IN RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

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Progressive disease (PD) remains the main cause of treatment failure following reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) in Hodgkin lymphoma (HL) [1]. The disease progression rate has been reported to be 41% and 58.7% at one and five years, respectively, in a recent large registry analysis [2]. Similar data have been published by individual centers or groups [3,4]. Prognostic factors for PD have been identified, including chemorefractory disease, extent of prior therapy and early relapse (i.e. within six months) following a prior autologous SCT (auto-SCT) [2]. Lowering the incidence of PD is essential for the long-term success of allo-SCT. This could conceivably be accomplished using a novel preparative regimen capable of providing more effective cytoreduction. The addition of new and active agents (particularly against HL) may be required in order to improve on the ones currently employed.

Gemcitabine is an analogue of deoxycytidine which has been shown to be active as single agent in a variety of solid tumors [5]. It is also known to be a highly effective agent in relapsed and refractory HL, both as a single agent as well as in chemotherapy combinations [5,6]. As a single agent, its overall response rate in heavily pretreated HL patients was reported to be 39% [6]. Serious non-hematologic toxicities are fairly uncommon but pulmonary, cutaneous and mucosal toxicities have been described [6–8]. Gemcitabine has been incorporated in conditioning regimens for auto-SCT in HL [9]. With regard to RIC for allo-SCT, while the drug has been employed in the contest of solid (i.e. pancreatic) tumors [10], it has not been investigated in the contest of HL. Preclinical studies have suggested a possible synergism between gemcitabine and fludarabine [11], the latter being the backbone

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of most current RIC regimens. For these reasons, we assessed the addition of gemcitabine (G) to our standard fludarabine (FLU) - melphalan (M) RIC regimen in patients with relapsed and refractory HL undergoing allo-SCT, with the goal to improve cytoreduction and ultimately reduce the incidence of PD.

Study eligibility included a diagnosis of non-progressive HL, adequate organ function, no active or uncontrolled infection and an available matched related or unrelated stem cell donor. Prior exposure to gemcitabine did not disqualify patients from the trial. This study was approved by the University of Texas M.D. Anderson Cancer Center Institutional Review Board, and all patients provided written informed consent. This trial is registered at www.clinicaltrials.gov as NCT00385788. Regimen-related toxicities (RRTs) were graded according to NCI CTCAE v.3 (http://ctep.cancer.gov). Patients were considered evaluable for acute and chronic GVHD if they had achieved engraftment or survived at least until day 100 post transplant, respectively. Acute and chronic GVHD were graded as reported previously [4]. Chimerism was evaluated as described previously [4]. Actuarial rates of overall survival (OS), and progression-free survival (PFS) were estimated by the method of Kaplan-Meier [12].

Between 8/07 and 3/11, fifteen consecutive HL patients (UPN: Unique Patient Number) underwent an allo-SCT with the gemcitabine-fludarabine-melphalan (GFM) regimen (Table 1). They had failed multiple conventional treatments (median prior chemotherapy regimens: 4; range 2–9), radiation therapy (6/15; 40%) and a prior auto-SCT (6/15; 40%). The median age was 33 years (range 20–46). Disease status at SCT according to our previously published response criteria[4] was chemosensitive relapse (n=4), untreated relapse (n=1), induction failure chemosensitive (n=2), complete remission undetermined (CRU) (n=8). All patients but one (UPN 10) had previous exposure to gemcitabine in the salvage setting. The median time to PD after auto-SCT was 10 months (range 3–19). The donor was an HLA-identical sibling (n=10) or matched unrelated donor (MUD; n=5, with one donor being a 9/10 match for UPN 6).

The conditioning regimen consisted of G 800 mg/m^2 intravenously (IV) over 30 minutes x1 at day −7, FLU (32 mg/m^2 IV x4, day −5 to day −2), and M (70 mg/m^2 IV x2, day −3 and day −2). UPN 6 and UPN 7 received G 1000 mg/m^2 IV x2, day −5 and day −2. Thymoglobulin (4 mg/kg IV) was added in MUD allografts. Graft-vs-host disease (GVHD) prophylaxis included tacrolimus and mini-dose methotrexate (5 mg/m^2).

All patients achieved initial engraftment; one had graft rejection. Myeloid recovery was prompt, with an absolute neutrophil count (ANC) ≥ 500/μL at day +12 (range 11–20). Median platelet recovery at ≥ 20,000/μL was at day +14 (range 9–26). Chimerism studies on marrow or peripheral blood indicated 100% donor-derived engraftment in 13/13 evaluable patients (100%). Day 100/overall transplant-related mortality (TRM) were 2/15 (13%) and 2/15 (13%), respectively. Acute GVHD occurred in 8/14 (57%) patients, chronic GVHD in 7/13 (54%) patients (extensive in all of them) (Table I).

Selected RRTs such as pulmonary, cutaneous and mucosal are outlined in Table I. Pulmonary toxicity was experienced in four patients (26%). Grade 4 pulmonary toxicity

(bilateral pulmonary infiltrates with respiratory failure) was seen in one of the patients who received two doses of gemcitabine (UPN 6). Otherwise pulmonary toxicity was seen in three patients (grade 2 n=1; grade 1 n=2). It consisted of nonspecific and self-limiting findings such as pleural effusion, cough, and dyspnea, respectively. Cutaneous toxicity (usually in the form a skin rash, responsive to steroid therapy) was seen in five patients (33%: grade 3 n=1; grade 2 n=1; grade 1 n=3). Mucositis was seen in nine patients (60%). It was grade 3 in one patient (once again UPN 6). All other patients had either grade 2 (n=4) or grade 1 (n=4). It should be noted that the overall incidence of grade 1–4 pulmonary toxicity and mucositis in our historical experience with the FLU-M regimen were 19% and 45%, respectively, while cutaneous toxicity was rare [13].

Twelve patients are alive (nine progression-free, eleven in CR/CRU) with a median follow-up of 18 months (range 2–33). Three patients expired (graft rejection n=1, in the 9/10 MUD allograft UPN 6; viral pneumonia n=1; PD n=1). UPN 6 and 12 were not evaluable for response due to graft rejection and early death, respectively. (Table I).

Of the seven patients with active disease at study entry, three are currently in CR/CRU, although UPN 7 progressed and was reinduced into CR with radiation therapy. Among the other four, two expired before day +100 post transplant, one died due to PD and one progressed but is alive with stable disease. Among the eight patients transplanted while in CRU, all are presently alive and in CR, although UPN 5 progressed and was reinduced into CR with chemoradiotherapy. The favorable outcome of patients transplanted in CRU is in keeping with what has been reported previously [2–4]. Among the six patients with a prior auto-SCT (median number of prior chemotherapy regimens: 4, range 2–9), three (50%) are alive in CR/CRU, while eight (88%) of the nine patients without a prior auto-SCT (median number of prior chemotherapy regimens: 3, range 2–6) are alive in CR/CRU (Table I).

Actuarial rates of OS and PFS at 18 months are 87% (95% CI: 56–96) and 49% (95% CI: 18–74), respectively (Figure 1). OS and PFS estimates at 24 months are the same, as no events (progression or death) occurred between 18 and 24 months. While a formal and meaningful comparison with our previously reported experience with the FLU-M regimen is clearly not possible, OS and PFS (actuarial estimates) at 24 months were 64% (95% CI: 49–76), and 32% (95% CI: 20–45), respectively [4].

Gemcitabine was administered prior to the fludarabine-melphalan regimen (i.e. a sequential approach). The 800 mg/m^2 dose was selected as it is one of the most commonly used in chemotherapy combinations [5, 8]. Two patients (UPN 6 and UPN 7) received two gemcitabine doses with a higher cumulative dose of the drug. This was part of an attempt to dose-escalate the drug and evaluate the possibility of concomitant (as opposed to sequential) administration of gemcitabine and fludarabine-melphalan. One of these two patients (UPN 6) experienced severe multiorgan toxicities (along with graft rejection), so we elected not to pursue this further.

The concomitant administration of fludarabine and gemcitabine (with the latter given as a continuous infusion) was explored in a Phase I study in acute leukemia patients. Severe stomatitis or esophagitis proved to be the most common non-hematological dose-limiting

toxicity. The authors hypothesized a highly synergistic interaction between G and FLU at clinically achievable plasma concentrations [14]. The controversy surrounding the issue of short-term infusion vs. continuous infusion for gemcitabine has been recently reviewed [15].

Based on these data, the addition of G to FLU-M is feasible and appears promising for treatment of relapsed and refractory HL. Pulmonary and cutaneous toxicities, while clinically significant, were largely manageable and did not contribute to mortality in the patients treated with only one G dose. Mucositis did not appear to be dramatically different from our previous historical experience with the FLU-M regimen. Although quite encouraging, we acknowledge that these data are preliminary. The GFM regimen deserves further study in a larger cohort of patients. However, the planning of any future study will need to take into account the interaction between fludarabine and gemcitabine when administered concomitantly, as well as the gemcitabine dose rate [14,15].

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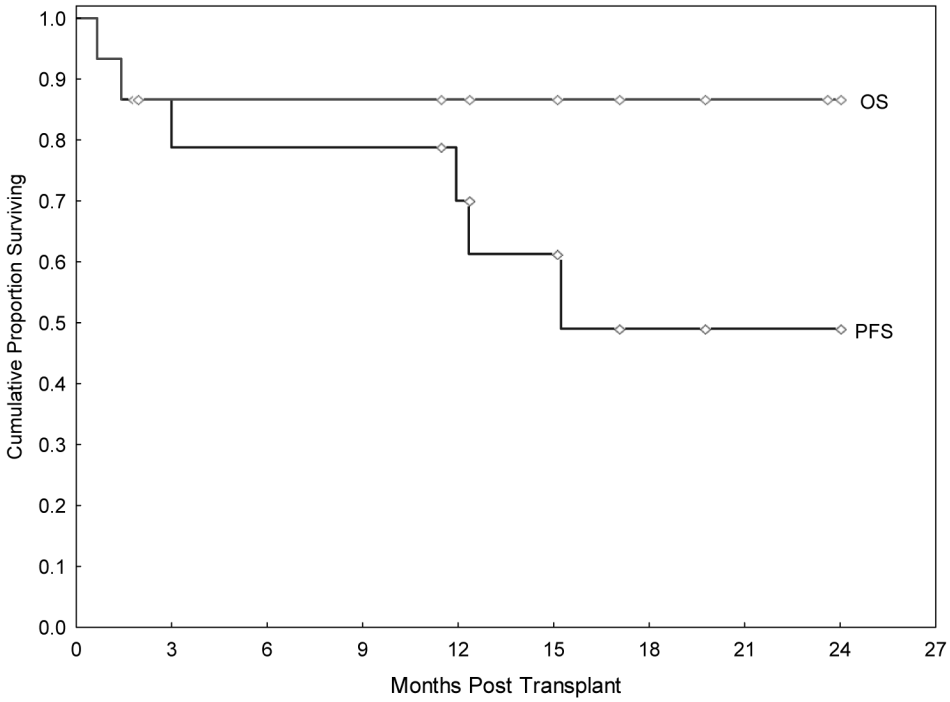

Figure 1.
Overall survival (OS) and progression-free survival (PFS) for the study group.

Table I

Patient characteristics, pretransplant status, regimen-related toxicities (RRTs), GVHD and patient outcome.

Patient (UPN)	Age at SCT	Prior chemotherapy regimens	Prior Auto-SCT (Y/N)	Donor Type	Stem Cell Source	Disease status at SCT	Pulmonary, skin and mucosal RRT (grade)	Acute GVHD (Y/N)	Chronic GVHD (Y/N)	Last Follow-Up After Allo-SCT and disease status	Cause of Death (if applicable)
1	26	9	Y	MUD	PBPC	Chemosensitive relapse	Pulmonary-1 Cutaneous-1	Y	Y	Day + 1047/Death	Progressive disease
2	34	3	N	MRD	PBPC	Induction failure, chemosensitive	None	Y	Y	Day + 1015/Alive, SD	
3	46	3	N	MRD	PBPC	CRU	None	Y	Y	Day + 950/Alive, CRU	
4	27	4	Y	MUD	BM	CRU	Pulmonary-1 Cutaneous-1 Mucositis-2	Y	Y	Day + 930/Alive, CR	
5	20	6	N	MRD	PBPC	CRU	Mucositis-1	N	Y	Day + 956/Alive, CRU	
6*	42	5	Y	MUD	BM	Chemosensitive relapse	Pulmonary-4 Cutaneous-3 Mucositis-3	N	NE	Day + 43/Death	Graft rejection
7*	37	3	N	MRD	PBPC	Chemosensitive relapse	Mucositis-1	Y	N	Day + 717/Alive, CRU	
8	31	4	N	MRD	PBPC	CRU	Cutaneous-1 Mucositis-1	Y	Y	Day + 600/Alive, CR	
9	25	3	N	MUD	BM	Induction failure, chemosensitive	Pulmonary-2 Cutaneous-2 Mucositis-2	Y	N	Day + 459/Alive, CR	
10	33	2	N	MRD	PBPC	CRU	N/A	N	Y	Day + 518/Alive, CR	
11	33	3	N	MRD	PBPC	CRU	Mucositis-1	N	N	Day + 348/Alive, CRU	
12	42	3	Y	MRD	PBPC	Untreated relapse	Mucositis-2	N	NE	Day + 20/Death	Cytomegalovirus pneumonia
13	20	2	Y	MUD	BM	CRU	Mucositis-2	Y	N	Day + 375/Alive, CRU	
14	38	3	N	MRD	PBPC	Chemosensitive relapse	None	NE	NE	Day + 58/Alive, CRU	
15	39	4	Y	MRD	PBPC	CRU	None	NE	NE	Day + 54/CRU	

UPN: unique patient number. Auto-SCT: autologous stem cell transplant. PBPC: peripheral blood progenitor cells; BM: bone marrow; MRD/MUD: matched related/unrelated donor;; GVHD: Graft-versus-host disease (Grade 2–4).

*UPN 6 and UPN 7 received two doses of gemcitabine.

NE: not evaluable. See reference [4] for response definitions for disease status at SCT, and text for GVHD and RRT grading.